Blood Levels of Omega 3 and 6 across the Progression of Alzheimer's Disease

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Background:
Previous studies have shown that Alzheimer's disease (AD) is characterised by significant alterations of omega6 and omega3 polyunsaturated chains (PC) incorporated in phospholipids. Investigating the dynamics of PC changes during the natural history of AD, in the brain as well as in the blood, is key for highlighting the role of fatty acids metabolism as therapeutic target. Current advances in disease progression modelling (DPM) allow estimating the long term temporal trajectory of AD biomarkers from collections of individual's observations acquired in clinical trials. Furthermore, these models enable the automatic staging of patients according to the measured biomarkers profile. In this study we leverage on DPM to model the changes of blood omega6/omega3 ratios across the natural evolution of AD estimated in clinical data.

Methods:
We considered the biomarkers measured over 5 years for a cohort of 808 individuals from the ADNI database, composed by clinical scores (ADAS,MMSE,FAQ), brain regional volumes (hippocampi,ventricles,entorhinal), and function (average glucose uptake from FDG- PET). We applied advanced disease progression modelling techniques [Lorenzi2017] to reconstruct the biomarker progressions spanning ~20 years (Figure 1). The relative individual staging was finally used to quantify the association between changes of blood concentrations ratios (omega6/omega3) and the disease progression.

Results:
Figure 2 reports the relationship between the individual disease stage and the ratios omega3/omega6 for the available **blood lipids** in the ADNI dataset (omega6: 20.4, 22:4, omega3: 20.5, 22.6). For all the considered cases there is a **significant inverse relationship** between the (log-) ratio omega3/omega6 and the individual stage identified by our model. This indicates that the increase of the individual biomarker severity (high disease stage) is **sistematically associated** with **an increase of the levels of omega6 with respect to the omega3** ($p<.01$ FDR correction for multiple comparisons).

Conclusions:
The dynamics of polyunsaturated fatty acids in the blood are significantly associated with the different progression stages of the pathology. The proposed statistical analysis allowed the identification of blood-based indices significantly associated with the progression of the pathology, and may lead to novel understanding of the role of fatty acids in neurodegeneration.

[Lorenzi2017] Lorenzi M., Filippone M., et al. NeuroImage, 2017

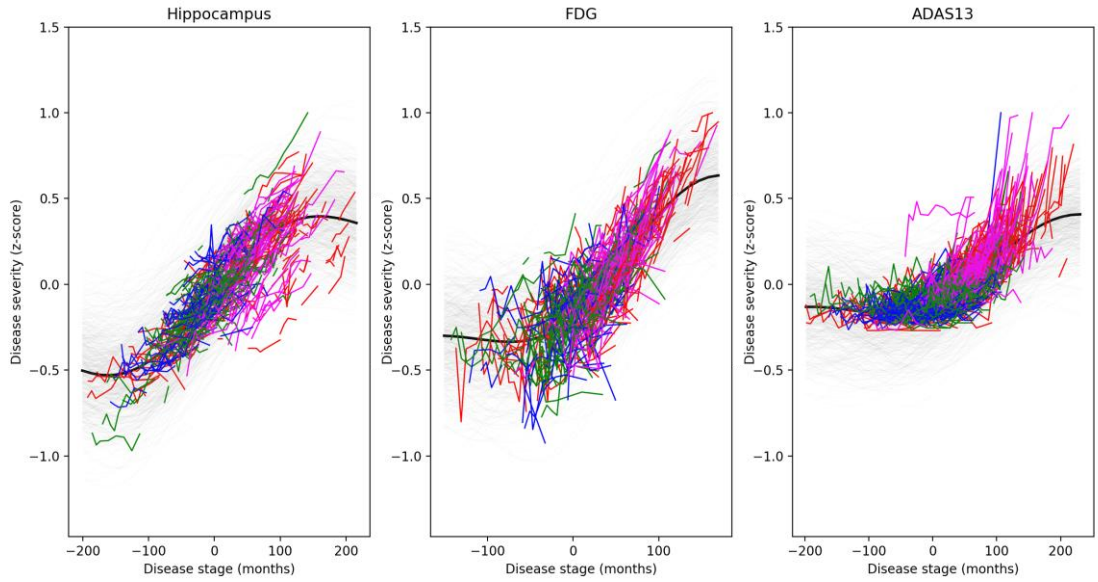

Figure 1. Estimated statistical model of biomarkers trajectories over time (black curves). The time span of the estimated biomarkers trajectories is of ~20 years. The spaghetti plot shows the individual biomarker measurements for healthy controls (blue), MCI stable (green), MCI converted to AD (purple), and AD patients (red). Grey curves: trajectory variability.

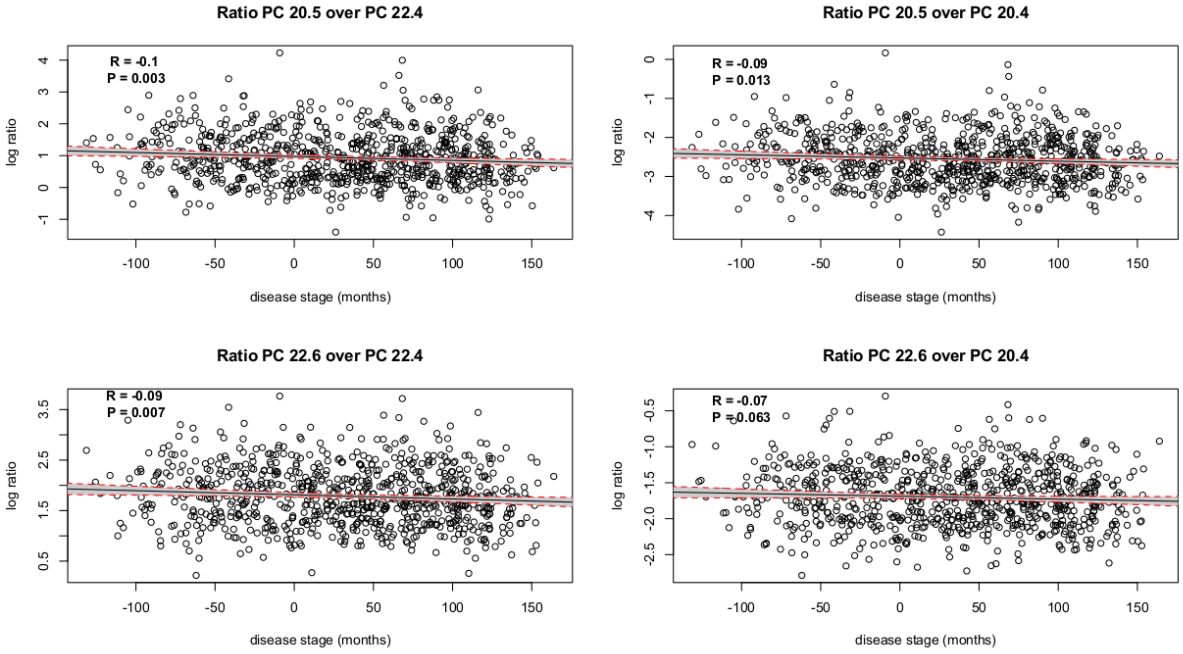

Figure 2. Relationship between the ratios of blood omega3 (PC 20.5, 22.6) and omega6 (PC 22.4, 20.4) and the disease stage associated with each individual. For all the considered cases there is a significant inverse relationship between the (log-) ratio omega3/omega6 and the individual stage identified by our model.